REACTION OF SUGAR 2-AMINO[1',2' : 4,5]OXAZOLINES WITH SUBSTITUTED ALKYL β-HALO- AND β-ALKOXYACRYLATES*

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2-Amino-β-D-arabinofuro[1',2':4,5]oxazoline (*I*) reacts in dimethylformamide in the presence of triethylamine with ethyl β-chlorocrotonate (*IIb*) and methyl β-chloro-β-ethylacrylate (*IIc*) with the formation of $O^{2,2'}$-anhydro-6-methyluridine (*Vb*) and $O^{2,2'}$-anhydro-6-ethyluridine (*Vc*), resp. Methyl β-chloro-β-tert-butylacrylate (*IId*), methyl β-chloro-β-phenylacrylate (*IIe*), ethyl β-bromomethacrylate (*IIe*), and methyl *cis*-β-bromoacrylate (*IIa*) do not react at all under analogous conditions. By refluxing of compound *I* in aqueous ethanol with ethyl β-ethoxyacrylate (*IIf*), there is obtained $O^{2,2'}$-anhydrouridine (*Va*) which is isolated after benzoylation with benzoyl cyanide as the 3',5'-dibenzoate *VIa*. Ethyl β-ethoxymethacrylate (*IIg*) does not react under analogous conditions. Ethyl β-chlorocrotonate (*IIb*) reacts in the presence of triethylamine with 2-amino-α-D-ribofuro[1',2':3,4]oxazoline with the formation of $O^{2,2'}$-anhydro-6-methyl-α-uridine (*VIII*) while $O^{2,2'}$-anhydro-1-[α-D-xylofuranosyl]-6-methyluracil (*IX*) is obtained from 2-amino-α-D-xylofuro[1',2':3,4]oxazoline.

Recently, considerable attention has been attracted by a novel synthesis of pyrimidine nucleosides consisting in reaction of sugar 2'-amino-1,2-oxazolines with acetylenic derivatives such as esters or nitriles of acetylenic carboxylic acids[1]. This reaction yields $O^{2,2'}$-anhydronucleosides of the uracil or cytosine series which serve as starting material in the preparation of 2'-deoxynucleosides[2-6] or ribonucleosides[7,8]. Investigations on the extent of the novel synthesis have been limited to modifications of the sugar component[2-6,9] and the acetylenic derivative[5,6]; the preparative importance of the method does not depend on the sugar derivatives which are accessible by reaction of the free sugar with cyanamide[1-4] but is limited by accessibility of the acetylenic derivative. It has been observed that the $O^{2,2'}$-anhydronucleosides of the uracil series are readily formed from esters of acetylenemonocarboxylic acid[1-4] and dicarboxylic acid[10] but less readily from esters of 2-butinoic acid[5,6]; the preparation of other substituted acetylenecarboxylic acids is rather difficult. By the use of acetylenecarboxylic acids, the scope of the reaction is limited to the preparation of nucleosides derived either from an unsubstituted uracil or from a 6-substituted uracil. In the literature however, an addition has been reported[11] of 2'-amino-1,2-oxazolines of the sugar series to the double bond of alkyl acrylates with the formation of cyclonucleosides of the 5,6-dihydrouracil series. The corresponding dehydrogenation to uracil derivatives is obviously difficult on the preparative scale though theoretically possible.

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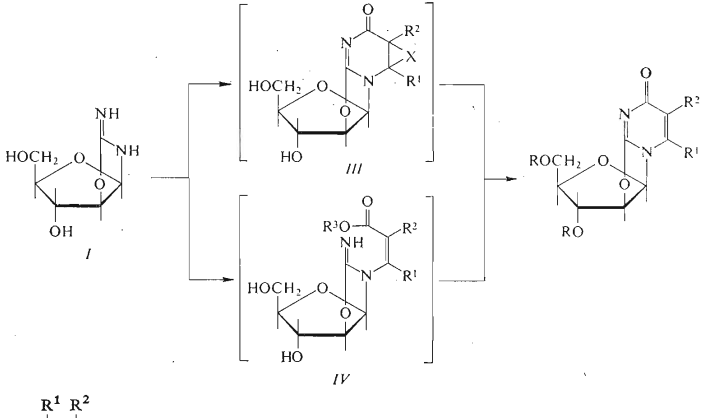
The aim of the present work was to examine the formation of $O^{2,2'}$-anhydrouridine derivatives (if any) from alkyl acrylates substituted at position β by a halo atom or by an ethoxyl group. In this case, the resulting addition products, *i.e.*, intermediates of the 5,6-dihydrouracil series, could readily eliminate one molecule of hydrogen halide or alkanol with the formation of the required compounds. An aminolysis of alkyl β-haloacrylates or β-alkoxyacrylates by reaction with the oxazoline NH group at position 1 and the subsequent ring closure of the acyclic intermediate to the uracil derivative represents an alternative explanation of the reaction course. The latter intermediate would be identical with that obtained in additions to acetylenic acids (Scheme 1).

Methyl β-bromoacrylate (*IIa*) was prepared from *cis*-β-bromoacrylic acid[12] by a successive treatment with thionyl chloride and methanol. As shown by NMR spectrum, no isomerisation took place during this reaction which consequently

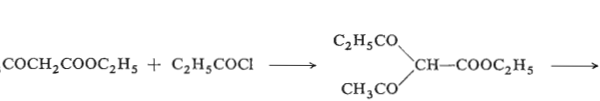


$$X-\underset{}{\overset{R^1}{C}}=\underset{}{\overset{R^2}{C}}-COOR^3$$

IIa, X = Br, $R^1 = R^2 = H$, $R^3 = CH_3$
IIb, X = Cl, $R^1 = CH_3$, $R^2 = H$, $R^3 = C_2H_5$
IIc, X = Cl, $R^1 = C_2H_5$, $R^2 = H$, $R^3 = CH_3$
IId, X = Cl, $R^1 = (CH_3)_3C$, $R^2 = H$, $R^3 = CH_3$
IIe, X = Cl, $R^1 = C_6H_5$, $R^2 = H$, $R^3 = C_2H_5$
IIf, X = Br, $R^1 = H$, $R^2 = CH_3$, $R^3 = C_2H_5$
IIg, X = OC_2H_5, $R^1 = R^2 = H$, $R^3 = C_2H_5$
IIh, X = OC_2H_5, $R^1 = H$, $R^2 = CH_3$, $R^3 = C_2H_5$
IIi, X = OC_2H_5, $R^1 = CH_3$, $R^2 = H$, $R^3 = C_2H_5$

V, R = H
VI, R = C_6H_5CO
a, $R^1 = R^2 = H$
b, $R^1 = CH_3$, $R^2 = H$
c, $R^1 = C_2H_5$, $R^2 = H$

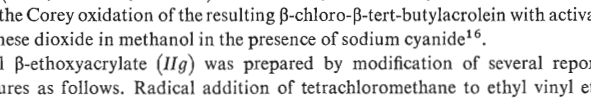
affords a pure *cis* ester *IIa*. Ethyl β-chlorocrotonate (*IIb*) was obtained by reaction of ethyl acetoacetate with phosphorus pentachloride in benzene[13]; the isomeric *cis* and *trans* esters *IIb* were separated under diminished pressure on a distillation column and isolated in pure state. Methyl β-chloro-β-ethylacrylate (*IIc*) was prepared analogously. Thus, ethyl acetoacetate was acylated with propionyl chloride and the resulting ethyl propionylacetoacetate converted by the action of sodium methoxide to methyl propionylacetate[14]; treatment of the latter ester with phosphorus pentachloride yielded the required compound *IIc*.



IIc

Methyl β-chloro-β-tert-butylacrylate (*IId*) was prepared by formylation[15] of pinacolone (methyl tert-butyl ketone) with dimethylchloromethyleneammonium chloride and the Corey oxidation of the resulting β-chloro-β-tert-butylacrolein with activated manganese dioxide in methanol in the presence of sodium cyanide[16].

Ethyl β-ethoxyacrylate (*IIg*) was prepared by modification of several reported procedures as follows. Radical addition of tetrachloromethane to ethyl vinyl ether afforded 1,3,3,3-tetrachloro-1-ethoxypropane which was not isolated but converted in refluxing ethanol to ethyl 3,3-diethoxypropionate; distillation of the latter ester with sodium hydrogen sulfate under diminished pressure afforded ethyl β-ethoxyacrylate[17,18] (*IIg*).



IIg

Ethyl β-chlorocinnamate[19] (*IIe*), ethyl β-bromomethacrylate[20] (*IIf*), ethyl β-ethoxymethacrylate[20] (*IIh*), and ethyl β-ethoxycrotonate[21] (*IIi*) were prepared by the earlier reported procedures.

Taking into account the experience from the earlier investigations (see above), the reactivity of unsaturated esters of the type *II* was examined under standard conditions with the use of the D-*arabino* compound *I* in refluxing anhydrous ethanol or in refluxing aqueous ethanol or dimethylformamide in the presence of triethylamine, at room temperature or at an elevated temperature. The composition of the reaction mixture was checked by chromatography. For the results see Table I.

From the present set of alkyl α- and β-substituted β-haloacrylates, only the β-methyl (*IIb*) and the β-ethyl (*IIc*) derivatives have been observed to react with compound *I* (*cf.* Table I). The reaction takes place in dimethylformamide in the presence of triethylamine at room temperature. The yield of the reaction of compound *I* with compound *IIb* is much higher (almost quantitative after prolonged reaction period of time) than with the tetrolate[5,6]. Increased temperatures may be in some cases accompanied by decreased yields of the products due to decomposition of the starting unsaturated compounds *II*. In aqueous or anhydrous ethanol either in the presence or in the absence of a tertiary base, the reaction does not take place. The derivatives of 6-methyluracil thus become readily accessible because of the easy accessibility of the ester *IIb*. Preparatively satisfactory yields may also be obtained with the use of the β-ethyl derivative *IIc* (to yield compound *V*) but not as high as with the ester *IIb*. Nevertheless, the 6-ethyluracil derivatives[8] are accessible by other methods with difficulty only. Both the *cis* and *trans* isomer of ethyl β-chlorocrotonate undergo the condensation to the uracil derivative *V*. In view of the intermediary presence of the acyclic type *IV* compound in the reaction mixture and occurence of triethylamine hydrochloride from the beginning of the reaction, it may be reasonably assumed that the reaction is initiated by substitution of the halo atom at position β in compounds *IIb* or *IIc* by the nucleophilic amino group at position 1 of compound *I*. The mechanism of substitutions of alkyl β-haloacrylates has not been fully elucidated. It may be assumed however, that compounds *IIb,c* react with the formation of an analogous

TABLE I
Reactions of Compound *I* with Esters *II*

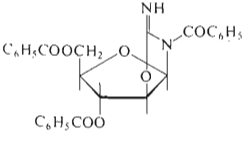
Ester	Method[a]	Product, %	Ester	Method[a]	Product, %
IIa	A, B, C	0	*IIe*	A, B, C	0[b]
IIb cis	A	*Vb*, 69	*IIf*	A, C,	0
IIb trans	A	*Vb*, 60	*IIg*	A, C, D	*VIa*, 24
IIc	A	*Vc*, 23	*IIh*	A, B, D	0
IId	A, B	0	*IIi*	A, C, D	0

[a] A: A mixture of compound *I* (1·0 g; 5·7 mmol), the ester *II* (15 mmol), dimethylformamide (5 ml), and triethylamine (2 ml) was stirred at room temperature and the reaction checked by withdrawals of samples for 7 days and chromatography in the solvent system S_1. B: The above mixture was heated at 80°C for 8 h under exclusion of atmospheric moisture. C: A mixture of compound *I* (1·0 g; 5·7 mmol), the ester *II* (15—20 mmol), and ethanol (20 ml) was refluxed for 8 h and analysed as above (A). D: Analogously to C but in ethanol containing various amounts of water (50—80%). [b] With the use of ethyl phenylpropiolate and methods A—D, no *V* was obtained.

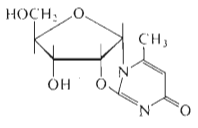
intermediate. On the other hand, an intermediary formation of an acetylenic ester cannot be excluded; it has been known that hydrogen halide is readily eliminated from compounds of the *IIb,c* type in contrast to the unsubstituted derivative of the *IIa* type[22]. Such an alternative explanation would be in accordance with the failure of compound *IIa* and the phenyl derivative *IIe* to react with compound *I*. It has also been demonstrated in a separate experiment that ethyl phenylpropiolate, the potential elimination product of ethyl β-chlorocinnamate (*IIe*), does not react with the oxazoline *I*. The non-reactivity of the tert-butyl derivative *IId* might be due to steric factors, *i.e.*, to the impossibility to form an anhydronucleoside of the *V* with a bulky tert-butyl group at position 6 of the heterocyclic nucleus. Steric factors, however, cannot play any role in the reaction of compound *I* with the methacrylate *IIf*; the failure to obtain compound *V* or the intermediary acyclic compound *IV* is obviously due to the impossible elimination of hydrogen bromide from ethyl β-bromomethacrylate (*IIf*) with the formation of the acetylenic derivative.

In contrast to reactions with alkyl β-haloacrylates occurring in the presence of a tertiary base and in aprotic media, none of the alkyl β-ethoxyacrylates *IIg*, *IIh*, and *IIi* reacts under these conditions with the sugar derivative *I*. The unsubstituted derivative *IIg* reacts in aqueous ethanol only to give the product in a low yield when compared with the reaction of the corresponding propiolate[1–6]. In this case it is advisable to separate the unreacted starting material from $O^{2,2'}$-anhydrouridine (*Va*) on treatment of the crude reaction mixture with benzoyl cyanide[23] which converts compound *Va* into the dibenzoate *VIa*; the latter dibenzoate is readily isolated because of its low solubility in ether or ethanol. From the preparative point of view, the use of the propiolate appears much more advantageous than that of the ester *IIg* but in large-scale preparations of compound *VIa*, the low price and accessibility of the ester *IIg* might assert itself[24].

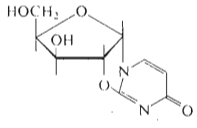
The mechanism of the formation of compound *Va* from the oxazoline *I* and the ester *IIg* remains obscure. Since, however, the benzoylated reaction mixture does not contain any further compounds in addition to the dibenzoate *VIa* and the perbenzoate *VII* of the starting compound *I*, an aminolysis of the vinylethereal function of com-



VII



VIII



IX

pound *IIg* might be involved, *i.e.*, a reaction proceeding *via* the intermediate of type *IV*, followed by cyclisation to the anhydronucleoside *Va*.

Since the formation of the anhydronucleosides *Vb,c* is preparatively advantageous, it was of interest to examine in this respect some additional types of 2'-amino-1,2-oxazolines. Thus, from the ester *IIb* and the α-D-*ribo* compound[1] there was prepared $O^{2,2'}$-anhydro-6-methyl-α-uridine (*VIII*) while $O^{2,2'}$-anhydro-1-(α-D-xylofuranosyl)--6-methyluracil (*IX*) was obtained from the α-D-*xylo* compound[4] (compounds *VIII* and *IX* were identical with authentic specimens[3,4]).

In the condensation of alkyl β-substituted β-haloacrylates with sugar 2'-amino--1,2-oxazolines, there may be obviously used additional acrylates bearing at position β alkyl groups of lower spatial requirements. Products of this condensation can be advantageously converted into the corresponding 6-substituted uridine derivatives, as reported elsewhere[8].

EXPERIMENTAL

Unless stated otherwise, the solutions were taken down on a rotatory evaporator at 35°C/15 Torr and substances were dried over phosphorus pentoxide at 0·1 Torr. Melting points were taken on a heated microscope stage (Kofler block) and are not corrected. The NMR spectra were measured on a Varian HA-100 apparatus in hexadeuteriodimethyl sulfoxide unless stated otherwise. Paper chromatography was performed by the descending technique on paper Whatman No 1 in the solvent system S_1, 2-propanol–conc. aqueous ammonia–water (7 : 1 : 2). Thin-layer chromatography was carried out on ready-for-use Silufol UV_{235} (Kavalier Glassworks, Votice, Czechoslovakia) silica gel foils in the solvent systems S_2, ethanol–chloroform (5 : 95), and S_3, ethanol–chloroform (10 : 90).

Methyl β-Bromoacrylate[12] (*IIa*)

To a mixture of 48% hydrobromic acid (200 ml) and acetone (146 ml; 2 mol) there was added dropwise with ice-cooling bromine (960 g *i.e.* 306 ml; 12 gramatom), the whole stirred at 0°C for 1 h, and diluted with water (1 200 ml). The heavy oil was separated, dried over calcium chloride, and distilled under diminished pressure to afford 360 g (1·22 mol; 61%) of 1,1,3-tribromoacetone, b.p. 112—118°C/9 Torr; reported[12], b.p. 108°C/9 Torr. This product was added to a suspension of sodium hydrogen carbonate (700 g) in water (4 l), the whole stirred at room temperature for 4 h, filtered, and the filtrate washed with two 200 ml portions of ether. The aqueous phase was adjusted to pH 2 with dilute (1 : 1) sulfuric acid and extracted with five 200 ml portions of ether. The ethereal extract was dried over anhydrous magnesium sulfate, filtered, the material on the filter washed with ether, the filtrate and washings combined, and evaporated to dryness. The residual crystalline *cis*-β-bromoacrylic acid (102 g; 56%) was heated in thionyl chloride (180 ml) to 50°C until a vigorous reaction set in. The mixture was then refluxed (bath temperature, 100°C) under exclusion of atmospheric moisture (calcium chloride tube) for additional 2 h and evaporated under diminished pressure. The residual oil was coevaporated with benzene (100 ml) and then dissolved with ice-cooling in methanol (100 ml). The solution was kept at room temperature overnight, diluted with ether (500 ml), washed successively with two 100 ml portions of water, four 100 ml portions of saturated aqueous sodium hydrogen carbonate, and water (100 ml), dried over anhydrous magnesium sulfate, evaporated, and the residue distilled under diminished pressure

to afford 39 g (35%) of methyl *cis*-β-bromoacrylate, b.p. 60°C/11 Torr. For $C_4H_5BrO_2$ (165·0) calculated: 29·11% C, 3·05% H, 48·46% Br; found: 29·50% C, 3·15% H, 48·82% Br. NMR spectrum ($CDCl_3$): 3·78 p.p.m. (s, 3 H) $COOCH_3$; 6·62 (d, 1 H; $J_{H,H} = 8·0$) =C—H.

Ethyl β-Chlorocrotonate[13] (*cis* and *trans*) (*IIb*)

To a suspension of phosphorus pentachloride (740 g; 3·55 mol) in benzene (500 ml) there was added dropwise with ice-cooling over 90 min ethyl acetoacetate (500 ml; 3·8 mol), the whole stirred at 0°C for 1 h, filtered, and the filtrate treated dropwise over 30 min below 50°C with water (600 ml). The mixture was cooled down to 30°C, the organic layer set aside, the aqueous layer neutralised (ice-cooling and stirring) with 40% aqueous sodium hydroxide, and extracted with two 250 ml portions of benzene. The benzene layers were combined, washed with four 200 ml portions of saturated aqueous sodium hydrogen carbonate till neutral, dried over anhydrous magnesium sulfate, and evaporated under diminished pressure. The residual oil was combined with the residue from the original benzene layer and rectified on an 1 meter column under diminished pressure to afford 111 g (0·92 mol; 24·2%) of the *cis* isomer *IIb*, b.p. 67—71°C : : 12 Torr, and 170 g (1·41 mol; 37·2%) of the *trans* isomer *IIb*, b.p. 59°C/5 Torr.

Methyl β-Chloro-β-ethylacrylate[14] (*IIc*)

To a mixture of magnesium shavings (14·4 g), ethyl acetoacetate (156 g; 1·2 mol), and benzene (240 ml) there was added dropwise with stirring propionyl chloride (168 g; 1·84 mol) and the whole refluxed with stirring for 3 h under exclusion of atmospheric moisture (calcium chloride tube). After external cooling with ice, there was added to the mixture ice (500 g) and ether (500 ml), the whole filtered through Cellit, the organic layer separated, washed with four 200 ml portions of saturated aqueous sodium hydrogen carbonate till neutral and with water, dried over anhydrous magnesium sulfate, evaporated under diminished pressure, and the residue distilled to afford a fraction (110 g; 49%) of ethyl propionylacetate, b.p. 115—118°C/15 Torr. To this fraction there was added 2M methanolic sodium methoxide (340 ml) and methanol (60 ml), the whole kept at room temperature overnight, and evaporated under diminished pressure. The residue was diluted with ice-cold water (200 ml), adjusted to pH 2 with dilute (1 : 1) sulfuric acid, and extracted with four 100 ml portions of ether. The ethereal extract was washed with water, dried over magnesium sulfate, the ether evaporated, and the residue distilled under diminished pressure to afford 43 g (56%) of methyl propionylacetate, b.p. 70—72°C/10 Torr; reported[14], b.p. 68—80°C/15 Torr.

This methyl ester was added dropwise with ice-cooling to a mixture of phosphorus pentachloride (70 g; 0·34 mol) and benzene (100 ml) over 10 min and the whole stirred at 0°C for 1 h. Water was then added dropwise (100 ml) over 30 min, the benzene layer washed with four 50 ml portions of saturated aqueous sodium hydrogen carbonate till neutral, dried over anhydrous magnesium sulfate, evaporated, and the residue distilled unter diminished pressure to afford 25 g (0·167 mol; 56%, based on methyl propionylacetate) of the methyl ester *IIc*, b.p. 70—71°C/10 Torr. For $C_6H_9ClO_2$ (148·6) calculated: 48·49% C, 6·10% H, 23·80% Cl; found: 48·78% C, 6·66% H, 23·32% Cl.

Methyl β-Chloro-β-tert-butylacrylate (*IId*)

A. β-*Chloro*-β-*tert-butylacrolein*[15]. Phosphorus oxychloride (174 ml; 1·89 mol) was added dropwise to dimethylformamide (170 ml), the mixture stirred at room temperature for 30 min, cooled down, and treated dropwise at 0°C with pinacolone (76·5 g; 0·77 mol). The stirring was

continued at 70°C for 3 h and the mixture poured onto ice (1 kg) and sodium acetate trihydrate (900 g). The whole was allowed to warm to room temperature and extracted with three 500 ml portions of ether. The ethereal extract was washed with saturated aqueous sodium hydrogen carbonate till neutral and water, dried over anhydrous magnesium sulfate, evaporated, and the residue distilled under diminished pressure to afford 65·6 g (0·45 mol; 58·5%) of β-chloro-β--tert-butylacrolein as a colourless oil, b.p. 72—74°C/18 Torr.

B. *The ester* IId (*cf.*[16]). To a suspension of activated manganese dioxide[25] (485 g) in methanol (2 l) there was successively added with stirring β-chloro-β-tert-butylacrolein (65·6 g; 0·45 mol), sodium cyanide (100 g), and glacial acetic acid (60 ml). The mixture was kept at room temperature overnight, filtered through Cellit, the material on the filter washed with methanol, the filtrate and washings combined, and evaporated under diminished pressure. The residue was diluted with water (300 ml) and extracted with three 200 ml portions of ether. The extract was washed with water (100 ml), dried over anhydrous magnesium sulfate, evaporated under diminished pressure, and the residue distilled to afford 47 g (60%) of the ester *IId*, b.p. 102—104°C/15 Torr; reported[16], b.p. 203—204°C. For $C_8H_{13}ClO_2$ (176·6) calculated: 54·40% C, 7·41% H, 20·08% Cl; found: 55·19% C, 7·39% H, 19·50% Cl.

Ethyl β-Ethoxyacrylate (*IIg*)

A. *Ethyl* 3,3-*diethoxypropionate*[17]. Ethyl vinyl ether (200 ml; 2 mol) was added dropwise over 1 h at 50°C to a mixture of tetrachloromethane (450 ml) and azobisisobutyronitrile (1·5 g) and the whole refluxed for 5 h (after this period of time, the temperature of vapours rapidly raised from 50°C to 73°C). The reaction mixture was then cooled down, the tetrachloromethane evaporated under diminished pressure, the residue kept with ethanol (500 ml) at room temperature overnight and the next day refluxed for 8 h, and evaporated under diminished pressure. The residue was diluted with ether (500 ml), washed with saturated aqueous sodium hydrogen carbonate until neutral, dried over anhydrous magnesium sulfate, evaporated under diminished pressure and the residue distilled under diminished pressure to afford 235 g (1·23 mol; 61·5%) of ethyl 3,3-diethoxypropionate, b.p. 88—89°C/8 Torr; reported[17], b.p. 95—96°C/12 Torr. The product was homogeneous on gas chromatography.

B. *Ethyl* β-*ethoxyacrylate*[18] (IIg). A mixture of ethyl 3,3-diethoxypropionate (200 g; 1·05 mol) and sodium hydrogen sulfate (1·5 g) was refluxed at 12 Torr/100°C (bath temperature). The reaction manifested itself by the drop of vacuum to 25—30 Torr; after 2 h, the reaction was complete, as shown by gas chromatography. Distillation under diminished pressure afforded 141·5 g (93%) of ethyl β-ethoxyacrylate (*IIg*), b.p. 75—77°C/8 Torr; reported[18], b.p. 60°C/1·8 Torr. NMR spectrum ($CDCl_3$): 1·26 (t, 3 H; $J = 7·0$) $CH_2\underline{CH}_3$; 1·44 (t, 3 H; $J = 7·0$) $CH\underline{CH}_2CH_3$; (q, 2 H; $J = 7·0$) $OC\underline{H}_2CH_3$; 4·17 (q, 2 H; $J = 7·0$) $COOC\underline{H}_2CH_3$; 5·18 (d, 1 H, $J_{2,3} = 12·9$) $C\underline{H}$—$COOC_2H_5$; 7·58 (d, 1 H; $J_{2,3} = 12·9$) $C\underline{H}$—OC_2H_5. As indicated by this NMR spectrum, compound *IIg* is a pure *trans* isomer.

$O^{2,2'}$-Anhydro-6-methyluridine (*Vb*)

A. A mixture of compound *I* (10 g; 57 mmol), compound *cis-IIb* (15 g; 0·1 mol), dimethylformamide (50 ml), and triethylamine (20 ml; 15 g; 0·15 mol) was stirred at room temperature for 3 days in a stoppered flask, the triethylamine hydrochloride filtered off, and washed with toluene (30 ml). The filtrate and washings were combined, evaporated at 50°C/0·1 Torr, and the residue coevaporated under analogous conditions with three 25 ml portions of toluene to remove traces of dimethylformamide. The final residue was crystallised from ethanol (500 ml) to afford

the chromatographically (R_F 0·65 in S_1) homogeneous compound *Vb* (9·5 g; 69%), m.p. 213 to 215°C, $[\alpha]_D^{25}$ −34·3° (*c* 0·5; dimethylformamide). For $C_{10}H_{12}N_2O_5$ (240·2) calculated: 50·00% C, 5·03% H; 11·66% N; found: 49·83% C, 5·00% H, 11·69% N.

B. The reaction was performed analogously to paragraph *A* except for the use of *trans-IIb* instead of the *cis* isomer. Yield of the chromatographically homogeneous compound *Vb*, 8·2 g (60%), m.p. 214—215°C.

$O^{2,2'}$-Anhydro-6-ethyluridine (*Vc*)

A mixture of compound *I* (34·8 g; 0·2 mol), the ester *IIc* (44 g; 0·3 mol), dimethylformamide (200 ml), and triethylamine (60 ml; 43·2 g; 0·43 mol) was stirred at room temperature for 5 days, filtered, and the precipitate washed with dimethylformamide (20 ml). The filtrate and washings were combined, evaporated at 0·1 Torr/50°C, and the residue crystallised from ethanol (100 ml) to afford 23·6 g (46·5%) of compound *Vc*, m.p. 196—197°C. For $C_{11}H_{14}N_2O_5$ (254·2) calculated: 51·97% C, 5·54% H, 11·02% N; found: 52·05% C, 5·51% H, 10·78% N. UV spectrum (water): λ_{max} 222 nm (ε_{max} 7800) and 252 nm (9500). NMR spectrum: 1·15 (t, 3 H,) and 2·57 (q, 2 H, J = 7·1) CH_2CH_3; 3·24 (m, 2 H); 4·06 (m, 1 H; $J_{4',3'}$ = 2·1, $J_{4',5'}$ = $J_{4',5''}$ = 5·5) $H_{4'}$; 4·39 (br d, 1 H; $J_{3',4'}$ = 2·1) $H_{3'}$; 5·13 (d, 1H; $J_{2',1'}$ = 5·5) $H_{2'}$; 5·63 (br s, 1 H) H_5; 6·42 (d, 1 H, $J_{1',2'}$ = 5·5) $H_{1'}$.

$O^{2,2'}$-Anhydro-6-methyl-α-uridine (*VIII*)

A mixture of 2-amino-α-D-ribofuro[1′,2′:3,4]oxazoline[1] (10·0 g; 57·5 mmol), the ester *trans-IIb* (15·0; 0·1 mol), dimethylformamide (50 ml), and triethylamine (20 ml; 0·15 mol) was stirred at room temperature for 4 days and processed analogously to compound *Vb*. Crystallisation from ethanol (50 ml) afforded 3·4 g (23·5%) of the chromatographically (R_F 0·67 in S_1) homogeneous compound *VIII*, m.p. 250—252°C, $[\alpha]_D^{25}$ +127·5° (*c* 0·5; water). For $C_{10}H_{12}N_2O_5$ (240·2) calculated: 50·00% C, 5·03% H, 11·66% N; found: 50·59% C, 5·49% H, 11·25% N. NMR spectrum: 2·28 (d, 3 H, $J_{CH_3,H}$ = 1·1) 6-CH_3; 3·40—3·80 (s, 3 H) 2 $H_{5'}$ + $H_{4'}$; 4·11 (m, 1 H, $J_{3',2'}$ = 6·4) $H_{3'}$; 4·95 (t, 1 H) 5′-OH; 5·20 (t, 1 H; $J_{2',1'}$ = $J_{2',3'}$ = 5·3) $H_{2'}$; 5·71 (d, 1 H) 3′-OH; 5·74 (d, 1 H) H_5; 6·36 (d, 1 H; $J_{1',2'}$ = 5·3) $H_{1'}$.

$O^{2,2'}$-Anhydro-1-(α-D-xylofuranosyl)-6-methyluracil (*IX*)

The reaction was performed analogously to compound *Vb* using 10 g (57·5 mmol) of 2′-amino-α-D-xylofuro[1′,2′:3,4]oxazoline[4] and 15 g (0·1 mol) of *trans-IIb* (reaction time, 3 days). Crystallisation from ethanol (50 ml) afforded 10·2 g (74%) of compound *IX*, m.p. 251—252°C; $[\alpha]_D^{25}$ +42·0° (*c* 0·5; water). For $C_{10}H_{12}N_2O_5$ (240·2) calculated: 50·00% C, 5·03% H, 11·66% N; found: 49·97% C, 5·04% H, 11·84% N. NMR spectrum: 1·15 (t, 3 H; J = 7·1) $CH_2C\underline{H}_3$; 2·57 (q, 2 H; J = 7·1) $C\underline{H}_2CH_3$; 3·24 (m, 2 H) 2 $H_{5'}$; 4·06 (m, 1 H; $J_{4',3'}$ = 2·1, $J_{4',5'}$ = 5·5) $H_{4'}$; 4·39 (br d, 1 H; $J_{3',4'}$ = 2·1) $H_{3'}$; 5·13 (d, 1 H; $J_{2',1'}$ = 5·5) $H_{2'}$; 6·42 (d, 1 H; $J_{1',2'}$ = 5·5) $H_{1'}$.

3′,5′-Di-O-benzoyl-$O^{2,2'}$-anhydrouridine (*VIa*)

A mixture of compound *I* (20 g; 0·115 mol), the ester *IIg* (50 ml), and 80% aqueous ethanol (250 ml) was refluxed for 8 h, cooled down, and evaporated under diminished pressure. The residue was triturated with ethanol (50 ml) and acetone (300 ml), the crude *Va* collected with suction, washed with acetone, and dried *in vacuo*. A suspension of the dry *Va* in dimethylformamide

(100 ml) was then successively treated with benzoyl cyanide (39 g; 0·3 mol) and triethylamine (5 ml), the whole stirred at room temperature for 1 h, and diluted with ether (500 ml). The precipitate was collected with suction, washed with ethanol (100 ml) and ether (200 ml), and dried *in vacuo*. Yield, 2·2 g (24·5%) of the dibenzoate *VIa*, m.p. 312°C; reported[23], m.p. 312°C. For $C_{23}H_{18}.N_2O_7$ (434·4) calculated: 63·59% C, 4·17% H, 6·45% N; found: 64·05% C, 4·25% H, 6·22% N.

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